REMARKS

Claims 1-13 are pending in this application. Reconsideration of the outstanding rejections is respectfully requested for the reasons that follow.

Amendments

Claim 1 is amended to delete "is disclosed" as an obvious typographical error and to add that the purity and yield of monomer are above certain respective minimum levels. Support can be found for the latter amendment, for example, on page 3, lines 1-2. In addition, the preamble is clarified to indicate the obvious: that the monomers are present in the mixture with the dimers or multimers or both. Claim 3 now recites IgE, which is exemplified at least in Figure 1. Additionally, claims 2 and 3 are amended to recite separately the serum albumin and the particular types of antibodies, respectively.

Rejection under 35 USC §112, second paragraph

Claims 1-13 are rejected under 35 USC §112, second paragraph, as being indefinite for various reasons.

First, claims 1-13 are deemed unclear in the recitation of "a method is disclosed". The wording "is disclosed" has been deleted from the preamble of claim 1 to clarify the claims.

Claims 2-3 are deemed unclear in the recitation of a monomer polypeptide in view of their inclusion of antibodies. An antibody is considered a monomer in the context of the application herein, as supported by at least two separate standard textbooks on antibodies, the relevant portions of which are enclosed with this Amendment:

(1) In Essential Immunology, Sixth Ed., by Ivan Roitt (Blackwell Scientific Publications, 1988), Chapter 3, p. 31, it is noted that the basic structure of an immunoglobulin is a four-peptide unit, i.e., two identical heavy and two identical light chains held together by interchain disulfide bonds. See the antibody model given in Figure 3.1 on p. 31. See also p. 40, Table 3.2, which specifies the physical properties of major human immunoglobulin classes.

(2) In Antibodies, a Laboratory Manual, by Ed Harlow and David Lane (Cold Spring Harbor Laboratory, 1988), Chapter 2, p. 7, it is stated that

> [s]tructurally, antibodies are composed of one or more copies of a characteristic unit that can be visualized as forming a Y shape (see Fig. 2.1). Each Y contains four polypeptides--two identical copies of a polypeptide known as the heavy chain and two identical copies of a polypeptide called the light chain. Antibodies are divided into five classes, IgG, IgM, IgA, IgE, and IgD, on the basis of the number of Y-like units and the type of heavy-chain polypeptide they contain.

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Further, on page 10, it is stated that the various classes of antibodies may differ in the number of Y-like units that join together to form the complete protein. The example given is IgM antibodies, which have five Y-shaped units held together with a so-called "J-chain" peptide. Table 2.1 on the same page outlines the different classes; in particular, IgG, IgE, and IgD are all composed of a single Y-shaped unit, IgM is five Y-shaped units, and IgA can be one, two, or three Y-shaped units.

Hence, the accepted definition of an antibody is a molecule made up of two identical heavy and two identical light chains held together by interchain disulfide bonds, or in another words, a monomer composed of four proteins held together by disulfide bonds. Claim 2 no longer recites antibodies, and claim 3 refers to claim 1 and only covers the IgG and IgE subclasses of immunoglobulins, not the IgM and IgA subclasses where the monomers are held together by peptide or protein chains rather than disulfide bonds.

In view of the claim amendments and remarks above, applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 USC §112, second paragraph.

Rejections under 35 USC §102(a) and (b)

Claims 1-2, 5-7, and 9-13 are rejected under 35 USC §102(b) as being anticipated by Yang *et al.*, Journal of Chromatography, A 743 (1996). According to the Examiner, Yang *et al.* teaches a method of purifying antibodies from a mixture containing dimers, multimers, or both by applying the mixture to an anion-exchange chromatography resin at various pH ranges and utilizes a linear gradient and an elution salt at a gradient slope of 0 to 500 mM.

Applicants respectfully traverse this rejection. On page 171 of Yang *et al.*, in the paragraph spanning both columns, it is pointed out that the existence of subclasses, the differences in glycosylation, and possible post-translational changes impose a great challenge for separating IgGs, as well as separating unmodified antibodies from those that have been modified and denatured during storage. On page 175, left column, Yang *et al.* opines that "one interesting point is that a narrower peak may not be better than a broader peak when trying to resolve multiple components which have closely related properties, such as IgGs (which contains both heterogeneity and subclasses)."

Thus, Yang *et al.* is not trying to separate monomers from dimers or multimers as instantly claimed, but rather to separate monomers from other types of monomers such as differently glycosylated or post-translationally different IgGs. This is also evident from the nature of the chromatograms of the IgGs shown in Figs. 1-4 and 7-9. It is noted that these peaks are not separate peaks

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but broad ones, doublets, or shoulders that do not reflect separation of monomers from dimers or multimers. Fig. 5 shows protein standards and Figs. 10 and 11 depict separation of IgG from albumin, two totally different proteins that are not related as monomers and dimers or multimers are related.

In view of all the differences between the instant claims and the disclosure of Yang *et al.*, applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-2, 5-7, and 9-13 under 35 USC §102(b) over Yang *et al.*

Claims 1, 2, 5, and 8-13 are rejected under 35 USC §102(a) as being anticipated by Hahn *et al.*, Chromatography, 795, 277-287 (1998). The Examiner asserts that Hahn *et al.* teaches a method of separating polypeptide monomers from a mixture wherein the method comprises applying the mixture to a cation-exchange chromatography resin with pHs from 4.7 to 5.4. The Examiner further notes that the method of Hahn *et al.* utilizes a stepwise gradient and sodium chloride as the elution salt.

Actually, and with all due respect, Hahn *et al.* teaches separation of different proteins in bovine whey, such as IgG, lactoferrin, and lactoperoxidase (see, e.g., Table 1 on page 280). They do not discuss separation of a polypeptide monomer from its dimers and/or multimers as instantly claimed. Hence, there is no anticipation by Hahn *et al.*, and accordingly, applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 USC §102(a) over this reference.

Claims 1, 5, 7, 9, and 11-13 are rejected under 35 USC §102(b) as being anticipated by US Pat. 4,765,903 (D'Andrea *et al.*). The Examiner alleges that the process described in D'Andrea *et al.* involves separating a polypeptide monomer from a mixture containing dimers by cation exchange at a pH of 5.2 and eluting the mixture on any sodium gradient between 200 nM and 1 M.

The process of D'Andrea *et al.* requires three steps, reverse phase chromatography, cation-exchange chromatography, and gel filtration, to purify monomer from dimer. See Fig. 2 and especially Fig. 2(D), which shows that the fraction from the cation-exchange resin called FMM_2 (a monomer) still has dimer in it that is separated only by following the last step, gel filtration. See also Example I, col. 7, lines 33-35, which states that the two resolved peaks emerging from the gel filtration column represent dimers and FMM_2. Hence, the cation- exchange resin step did not actually separate dimers from at least one of the monomers, namely FMM_2.

In contrast, present claim 1 as amended, upon which all other rejected claims depend, specifies that the instant process consists essentially of the

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ion-exchange step, because that is the step that removes the dimers and multimers from the monomer; other steps are not required to accomplish this task. In addition, present amended claim 1 specifies yields of monomer of greater than 90%, whereas in Table I in col. 7 of D'Andrea et al., the percent recovery (or yield) of monomer (fast moving monomer FMM_2) for the cation-exchange step is only 31.1%.

In view of these distinctions between the process of instant amended claim 1 and that of D'Andrea, reconsideration and withdrawal of the rejection of the claims under 35 USC §102(b) over D'Andrea *et al.* is respectfully requested.

Rejections under 35 USC §103

Claims 1-2 and 4-13 are rejected under 35 USC §103(a) as being unpatentable over Yang *et al.* in view of US 4,764,279 (Tayot *et al.*). According to the Examiner, Yang *et al.* fails to teach separation of the specific polypeptide BSA from a mixture comprising dimers, but Tayot *et al.* teaches an anion-exchange method of separating albumin from a mixture comprising dimers.

The deficiencies of Yang *et al.* are discussed above and reiterated by noting that Yang *et al.* does not disclose and would not have suggested monomer/dimer±multimer separation as instantly claimed, but rather describes monomer/monomer separation or separation of two different proteins. Tayot *et al.* fails to compensate for the deficiencies in Yang *et al.* because it does not teach and would not have suggested separation of albumin from dimers as the Examiner asserts, but rather teaches separation of hemoglobin, gamma-globulins, and albumin from each other (see, e.g., claim 1) or hemoglobin and albumin from each other (see, e.g., claim 10). These protein moieties are not related as monomers and dimers and/or multimers as is required in the instantly claimed method.

Hence, these two references represent non-analogous art that is irrelevant to the currently claimed art of separating monomers from dimers and/or multimers. However, even if they were analogous, they would not have provided, alone or in combination, the necessary information and guidance to achieve the unexpectedly high minimum purity and yield levels claimed by applicants, e.g., greater than 99.5% and greater than 90% respectively.

In view of the large number of differences between the references and the instant claims as well as the unexpected results achieved by the present invention, reconsideration and withdrawal of the rejection of the claims under 35 USC §103 over Yang *et al.* in view of Tayot *et al.* is respectfully requested.

Claims 1-3 and 5-13 are rejected under 35 USC §103(a) as being unpatentable over Yang *et al.* and Hahn *et al.* in view of the Oncogene Science catalog 1992, pages 18 and 35.

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The Examiner acknowledges that Yang *et al.* and Hahn *et al.* fail to teach the specific antibodies claimed, but asserts that the Oncogene Science catalog teaches that numerous oncogenes, growth factors, and CD antibodies are known and that it is desirable to produce and purify them for industrial use.

The deficiencies in Yang *et al.* and Hahn *et al.* are noted above. The ordinary artisan of reasonable skill as of the effective filing date would have taken no disclosure from the catalog that would offset the deficiencies of the primary references, especially in view of the purity and yield recitations in present claim 1. The catalog, alone or in combination with the other references, would have provided no direction or motivation for the skilled practitioner in the relevant field at the time of filing to perform the monomer/dimer/multimer separation process set forth in claim 1, especially taking into account the unexpectedly high recited purity and yield levels recited and achieved by applicants. The references alone or in combination would not have addressed removing contaminants beyond the gross level of host cell proteins and DNA to the fine-tuned distinction among monomers, dimers, and multimers that the present claims address.

Hence, reconsideration and withdrawal of the rejection of claims 1-3 and 5-13 under 35 USC §103(a) as being unpatentable over Yang *et al.* and Hahn *et al.* in view of the catalog is respectfully requested.

It is believed that all the currently presented claims are in condition for allowance, and a notice to that effect is earnestly solicited. If the Examiner has any questions, she should feel free to call the undersigned attorney at the number indicated below.

Respectfully submitted,
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